

Drug Therapy During Pregnancy and the Perinatal Period

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Pregnancy Physiology Potentially Affecting Pharmacokinetics

- **Cardiovascular system**
 - Plasma volume expansion
 - Increase in cardiac output
 - Regional blood flow changes
- **Respiratory Changes**
- **Decrease in albumin concentration**
- **Enzymatic activity changes**
- **Increase in GFR**
- **Gastrointestinal changes**

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Cardiovascular System Changes

- **Plasma volume expansion**
 - Begins at 6 - 8 weeks gestation
 - Volume of 4700 - 5200 ml peaks at 32 weeks gestation
 - Increase of 1200 - 1600 ml above non-pregnant women

Cardiovascular System Changes

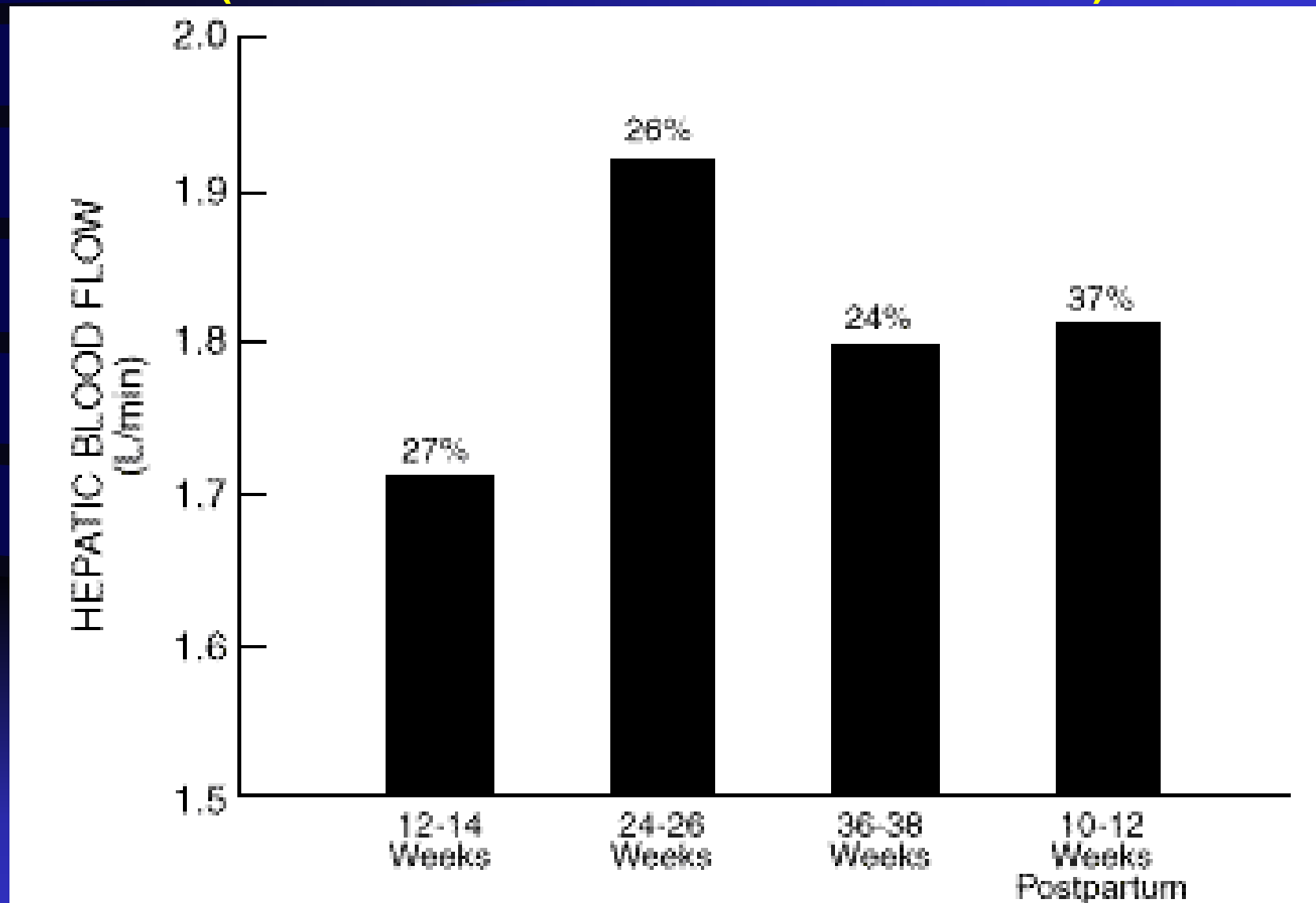
- **Cardiac output increases 30 - 50%**
 - 50% by 8 weeks gestation
- **Increase in stroke volume and heart rate**
 - Stroke volume in early pregnancy
 - Heart rate in later pregnancy

Regional Blood Flow Changes

- Increased blood flow to uterus - 20% of cardiac output at term
- Increased renal blood flow
- Increased skin blood flow
- Increased mammary blood flow
- Decreased skeletal muscle blood flow

HEPATIC BLOOD FLOW IN PREGNANCY

(IN L/min & AS % CARDIAC OUTPUT)



Robson SC, et al. Br J Obstet Gynaecol 1990;97:720-4.

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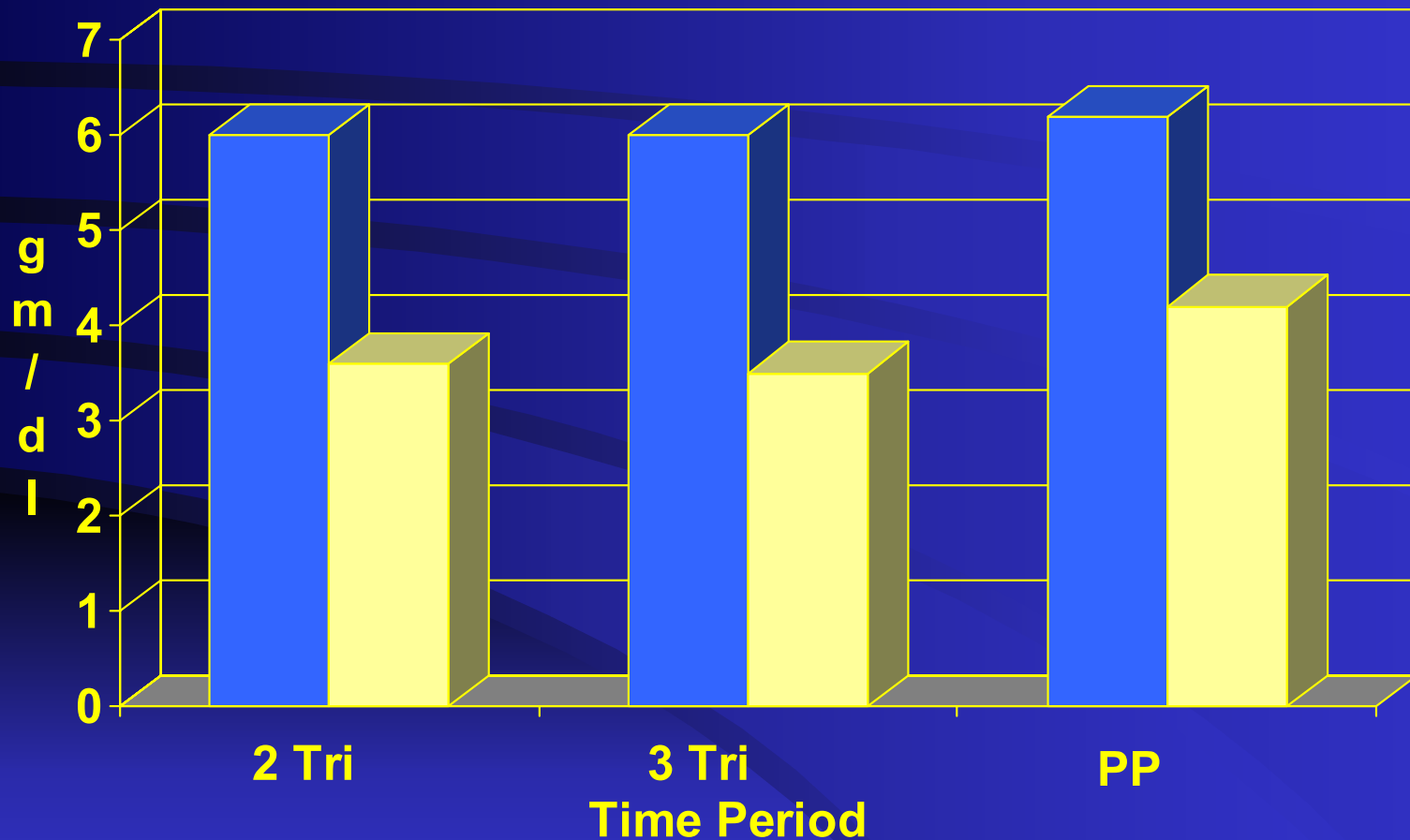
Respiratory Changes

- Compensated respiratory alkalosis
- Lowered $P_a\text{CO}_2$
- pH 7.44

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Albumin Concentration During Pregnancy



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- **Enzymatic activity changes**

Enzymatic Activity Changes

- Thought to be related to pregnancy hormonal changes
- N-demethylation inhibited by progesterone, not by estrogen

CYP3A4

- **Hydroxylation**
- **Increased activity during pregnancy**

CYP2D6 Activity

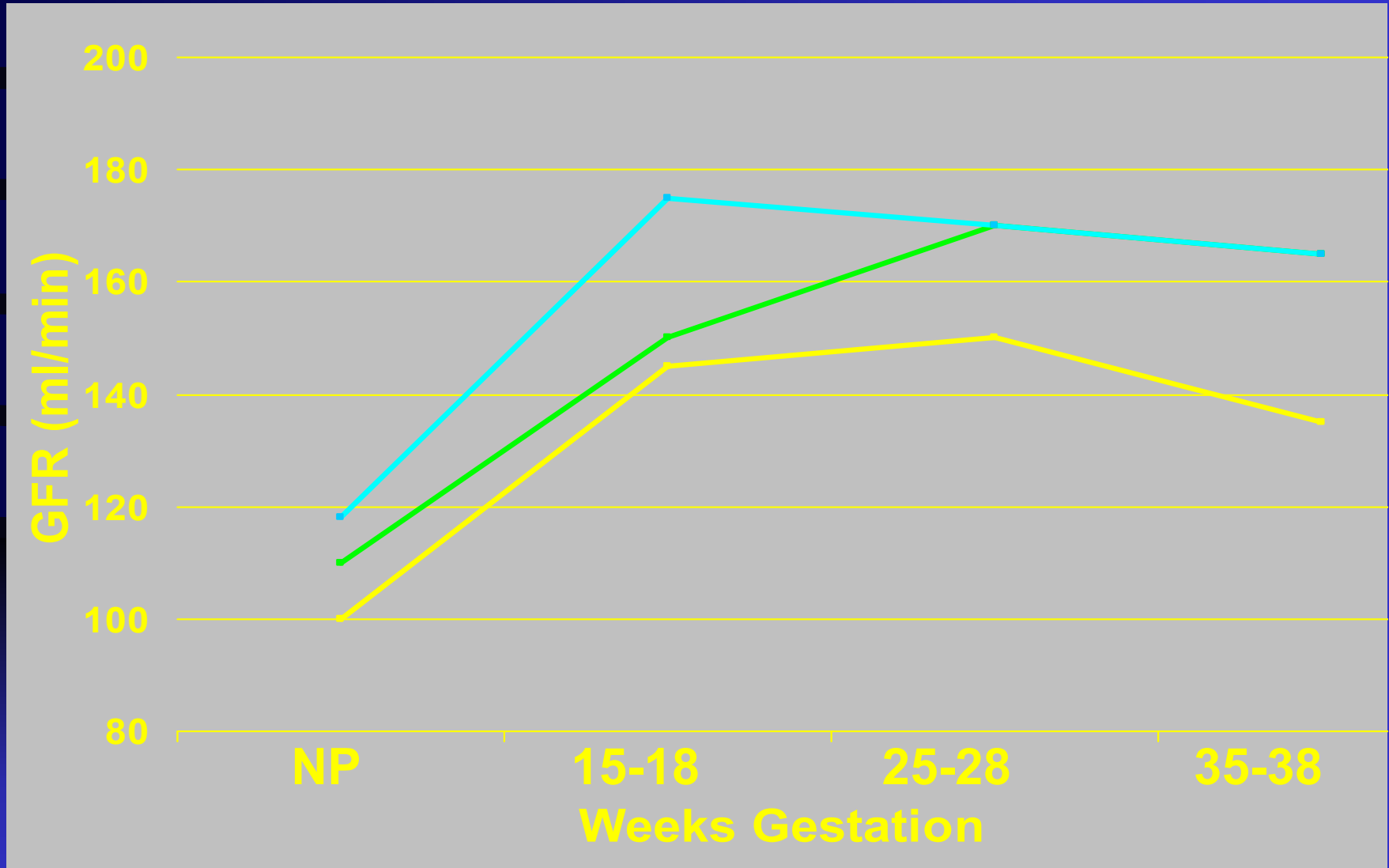
- Genetic determined polymorphism
- Increased clearance of metoprolol
- Decreased DM/D ratio in homozygous and heterozygous extensive metabolizers
- Increased DM/D ratio in poor metabolizers

Wadelius M, et al. Clin Pharmacol Ther 1997; 62: 400.

Pregnancy Physiology Potentially Affecting Pharmacokinetics

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- **Decrease in Albumin Concentration**
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- **Increase in GFR**

Renal Clearance Changes



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- **Enzymatic Activity Changes**
- **Increase in GFR**
- **Gastrointestinal Changes**

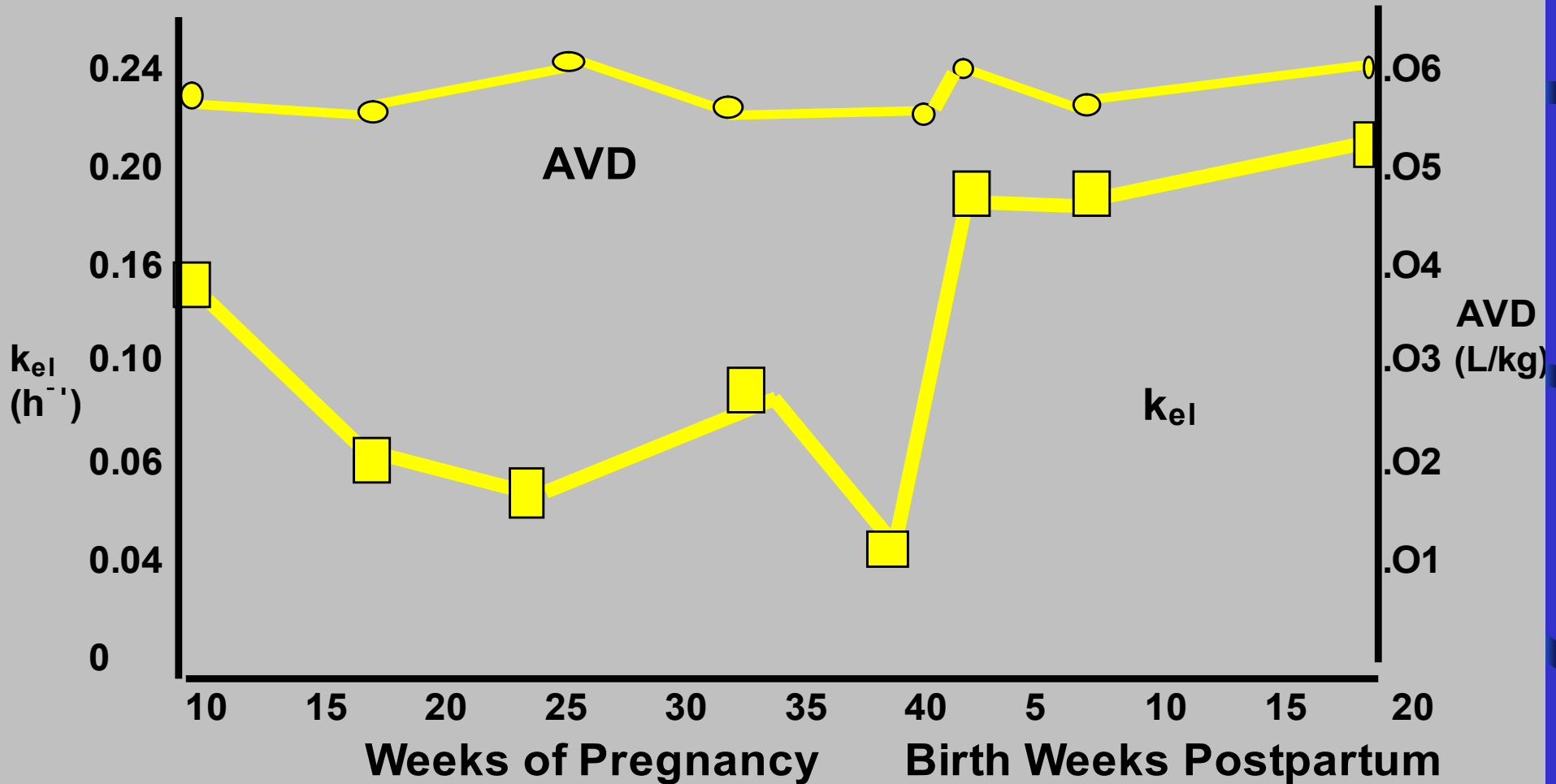
Gastrointestinal Changes

- **Decreased gastric acidity**
- **Delay in gastric emptying**
- **Increased transit time-progesterone effect**

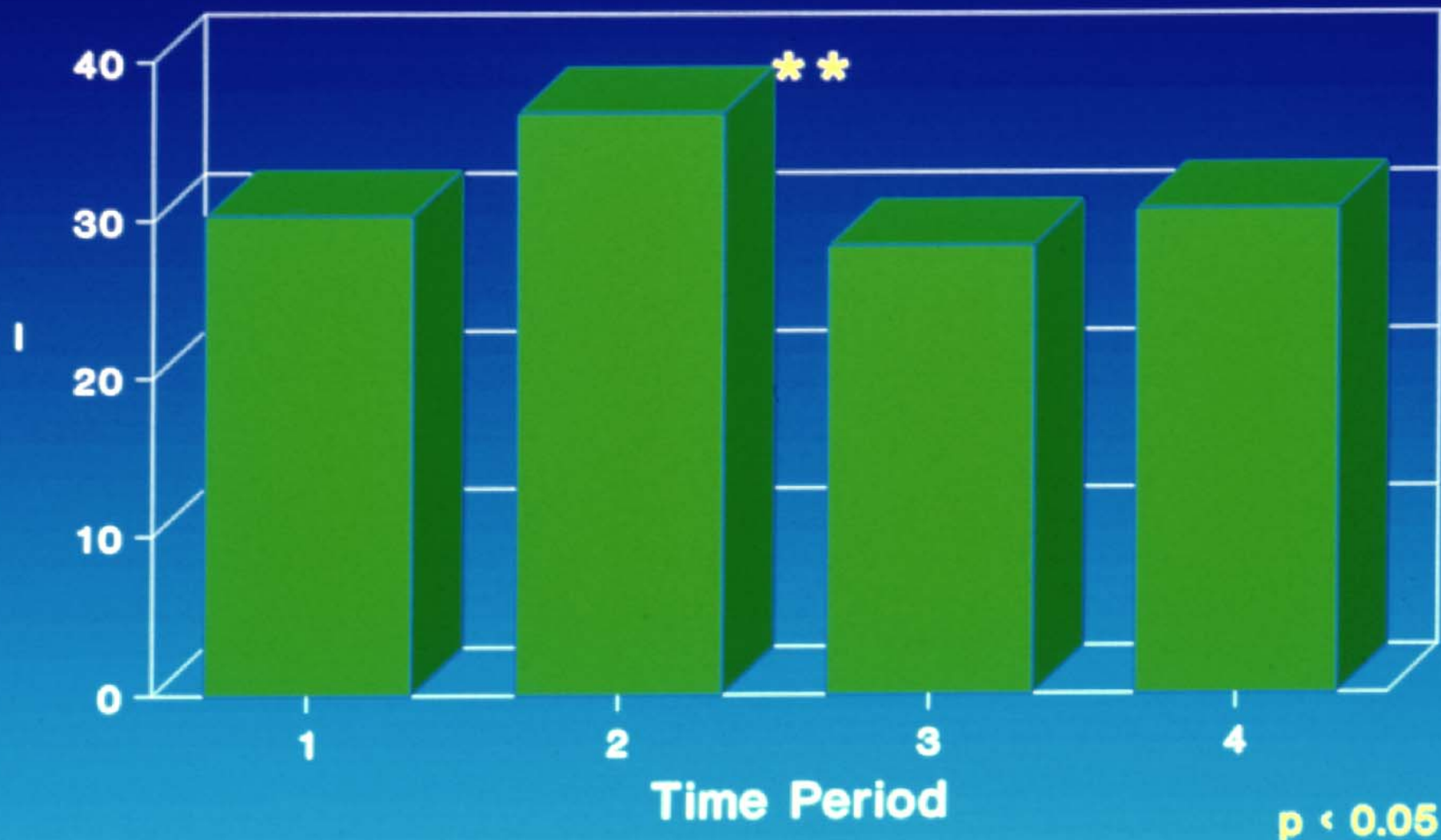
Maternal Physiologic Changes Altering PK of Drugs

- **Volume Expansion**

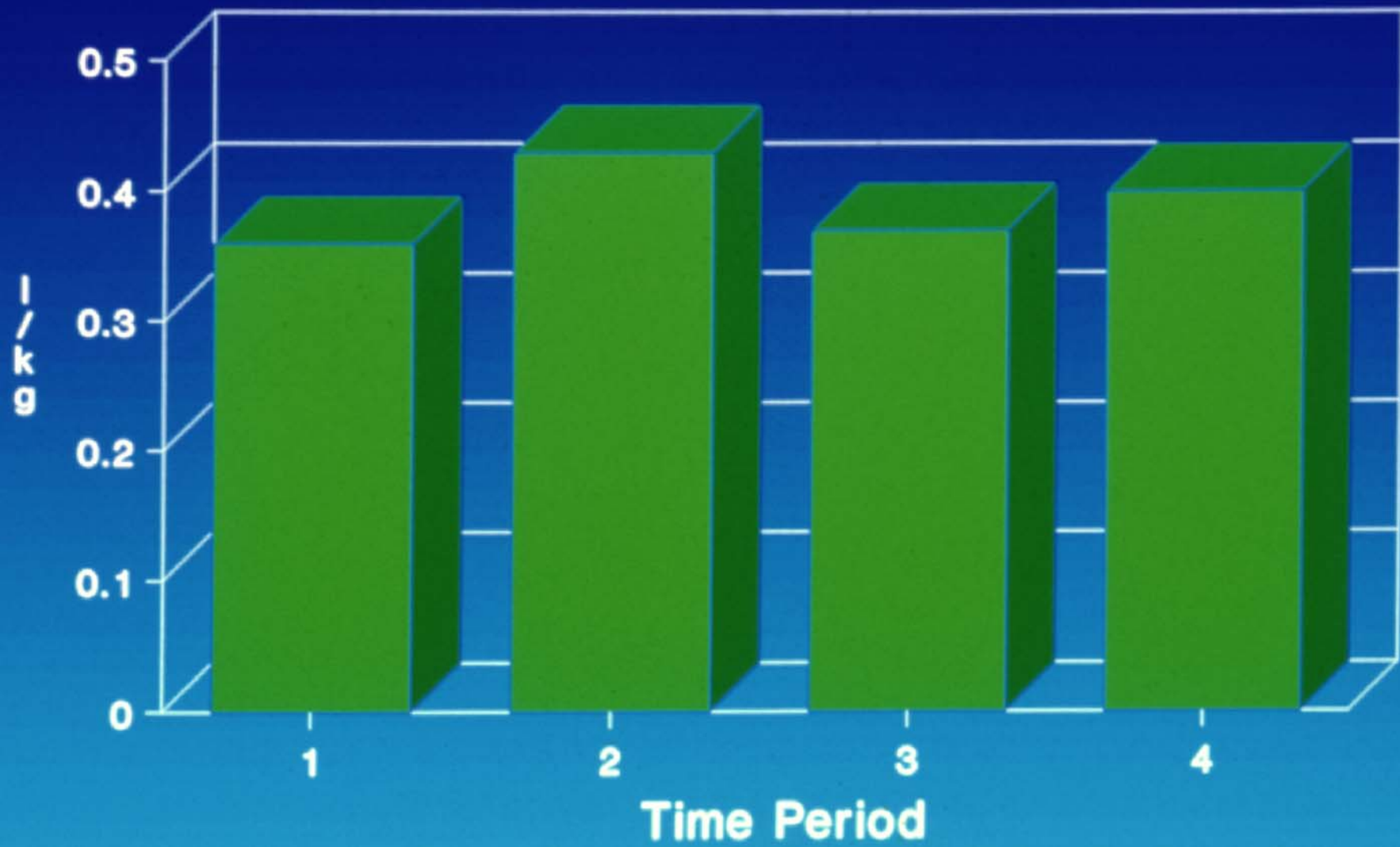
Caffeine Pharmacokinetics in Pregnancy



Theophylline Volume of Distribution During Pregnancy



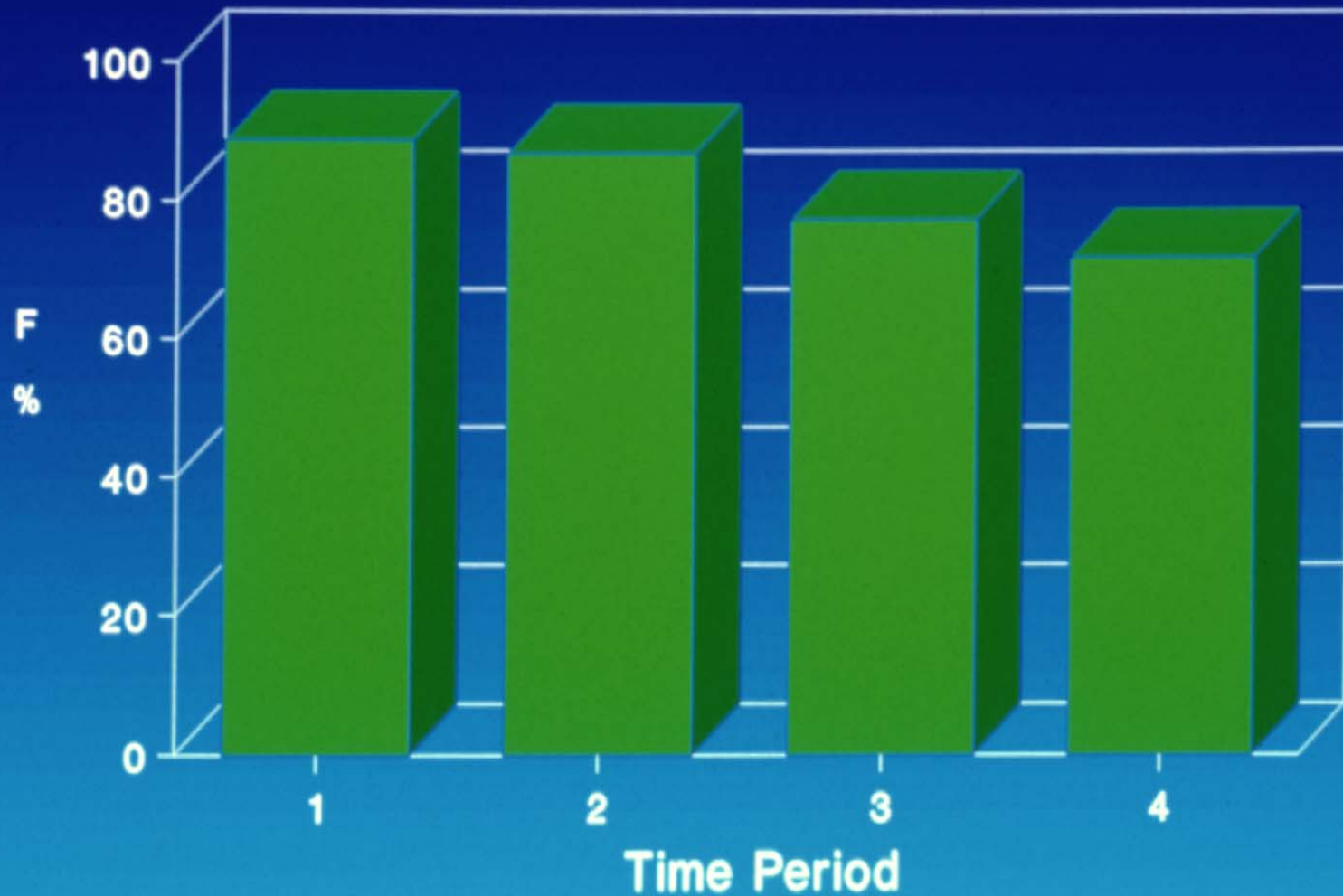
Theophylline Volume of Distribution During Pregnancy



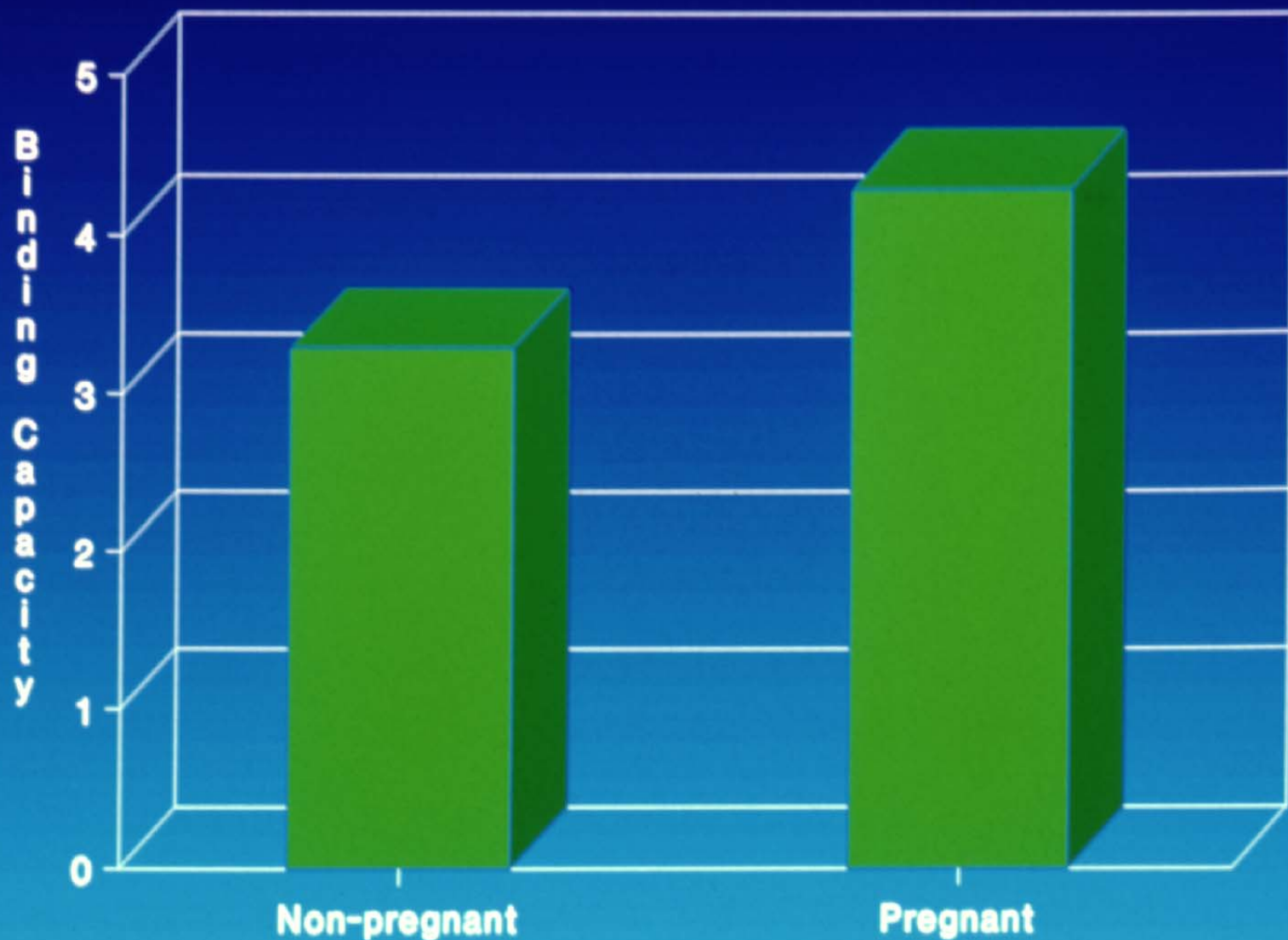
Maternal Physiologic Changes Altering PK of Drugs

- **Volume expansion**
- **Protein binding-increase in free fraction of drugs bound to albumin**

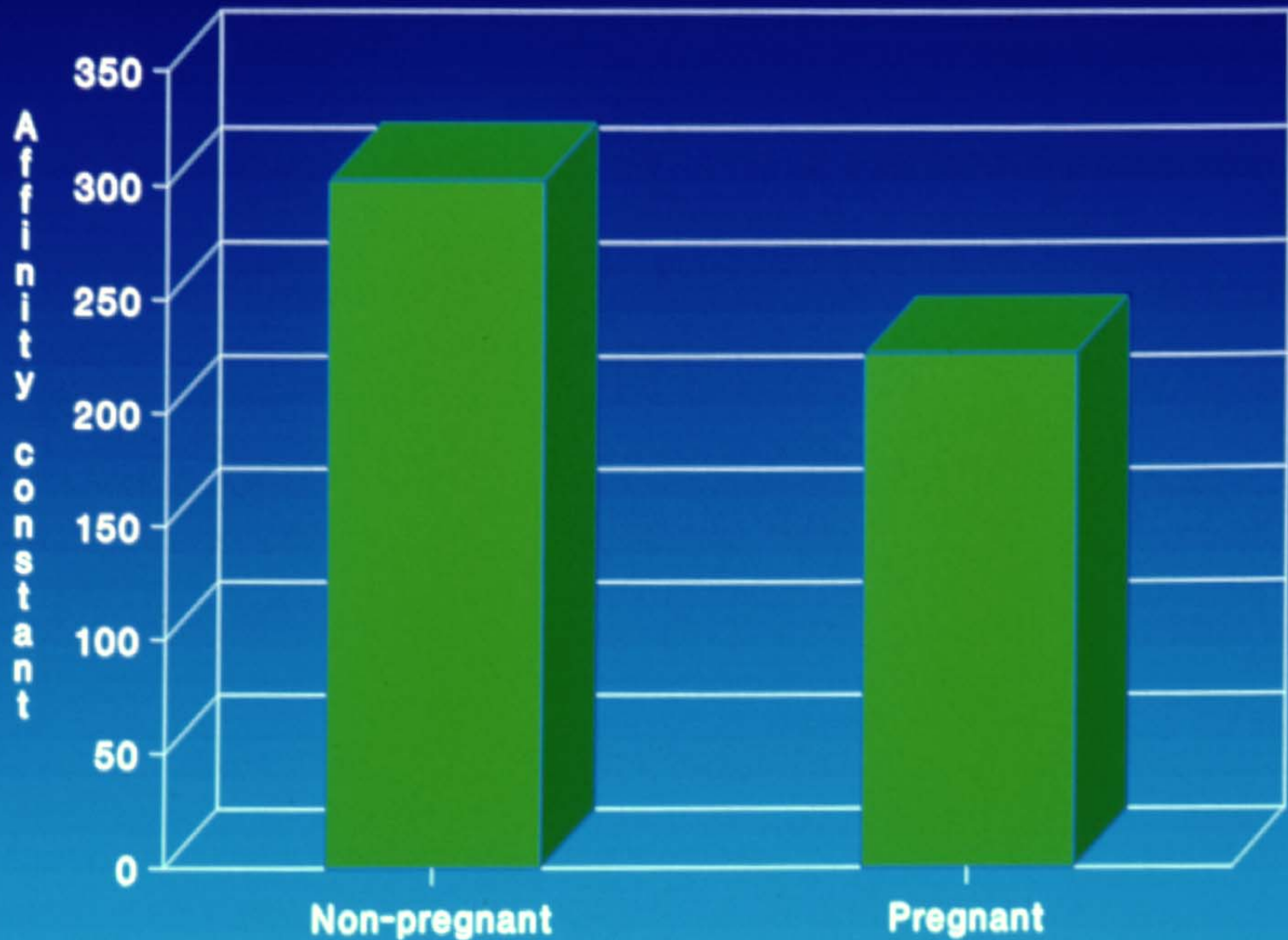
Theophylline Protein Binding During Pregnancy



Theophylline Protein Binding



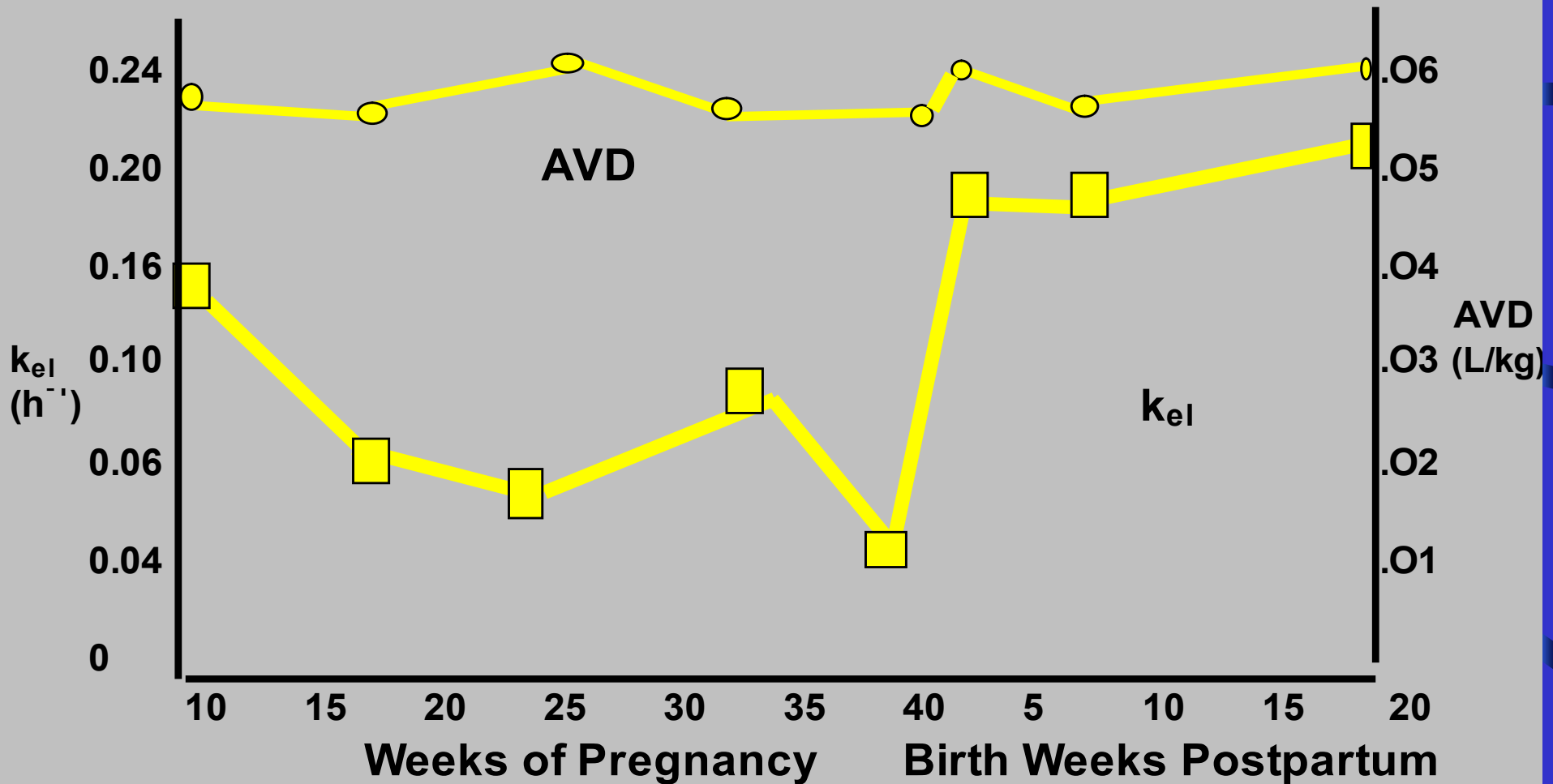
Theophylline Protein Binding



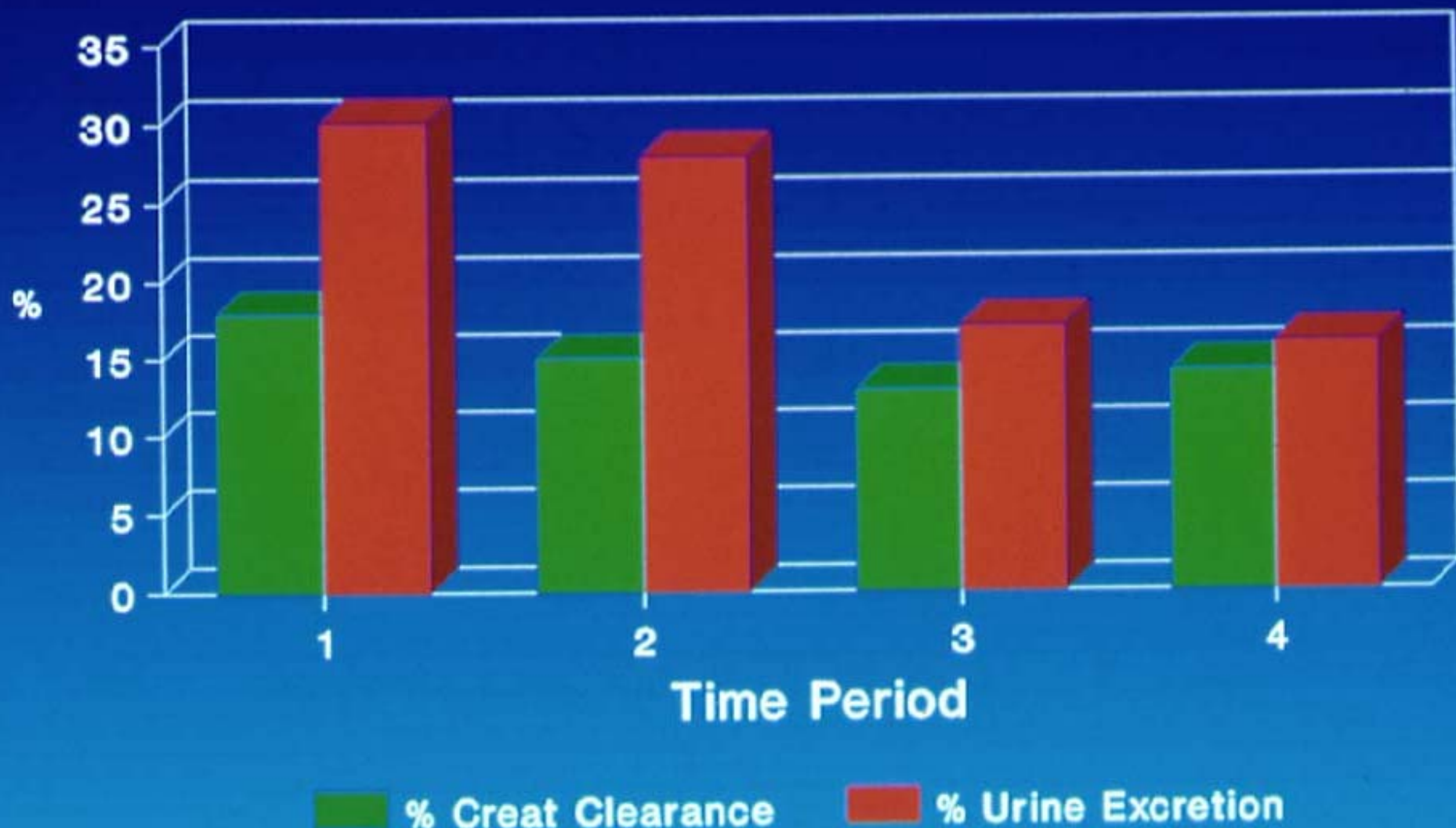
Maternal Physiologic Changes Altering PK of Drugs

- **Volume expansion**
- **Protein binding**
- **Clearance changes**

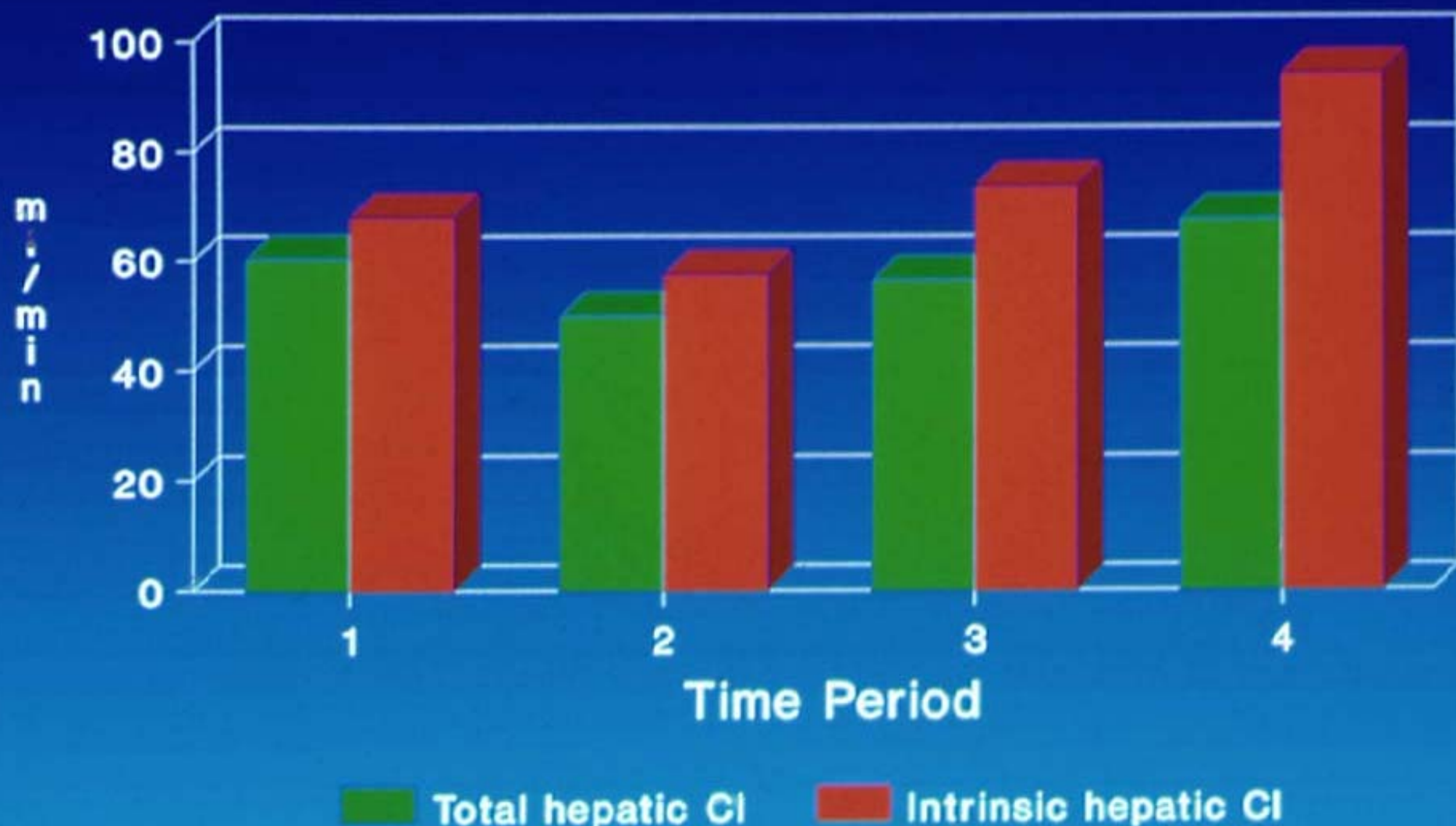
Caffeine Pharmacokinetics in Pregnancy



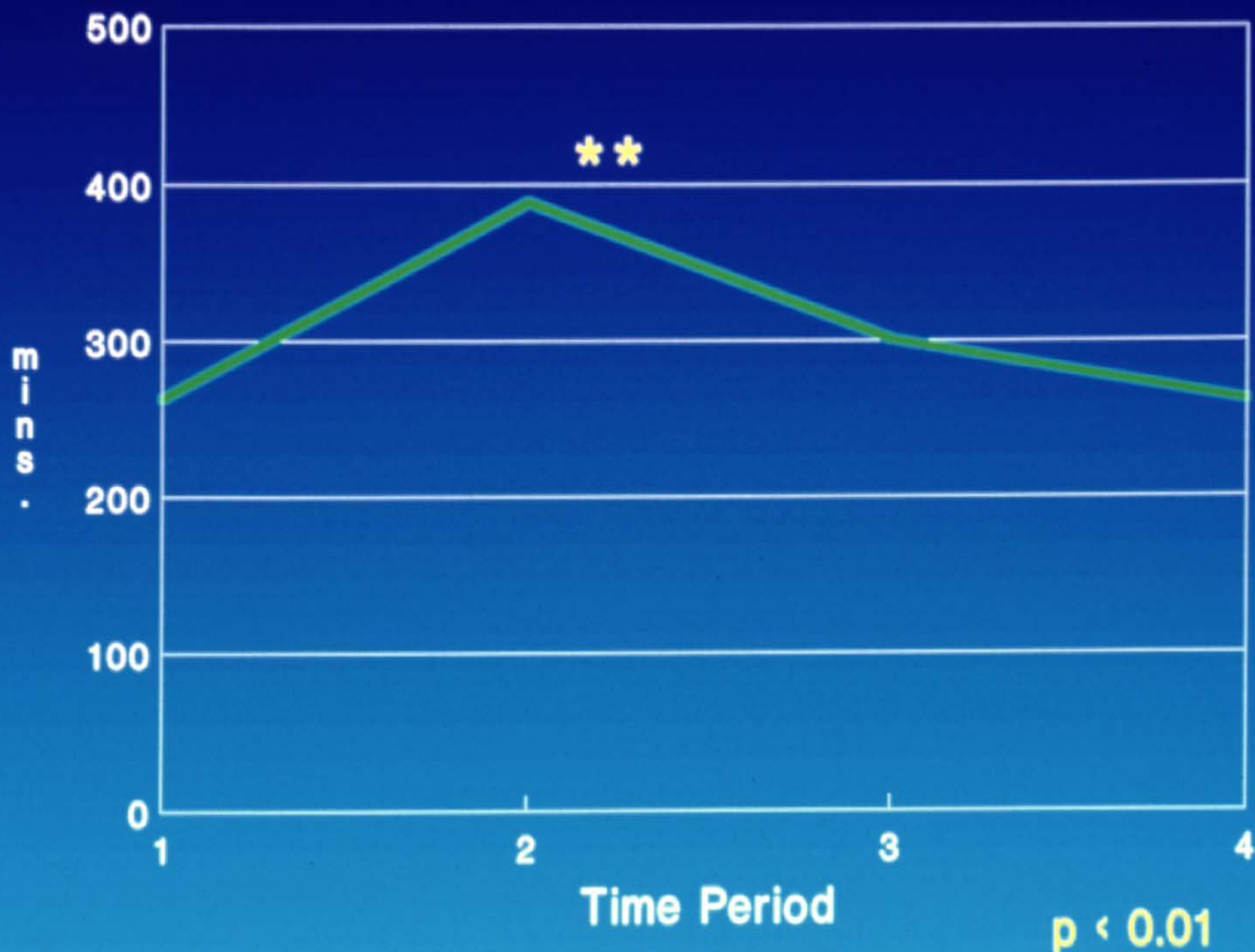
Theophylline Renal Clearance During Pregnancy



Theophylline Hepatic Clearance During Pregnancy

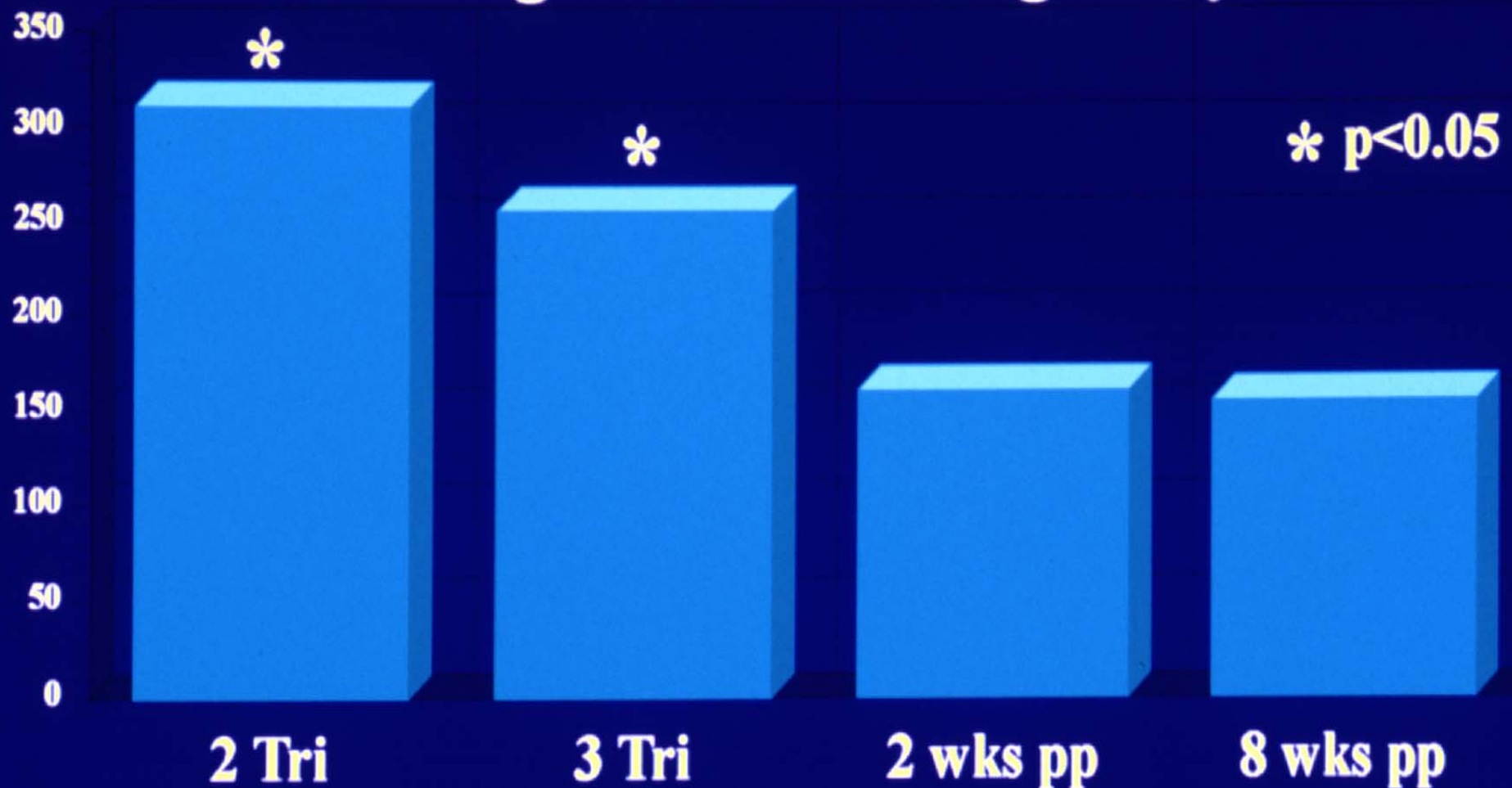


Measured Theophylline Half-Life



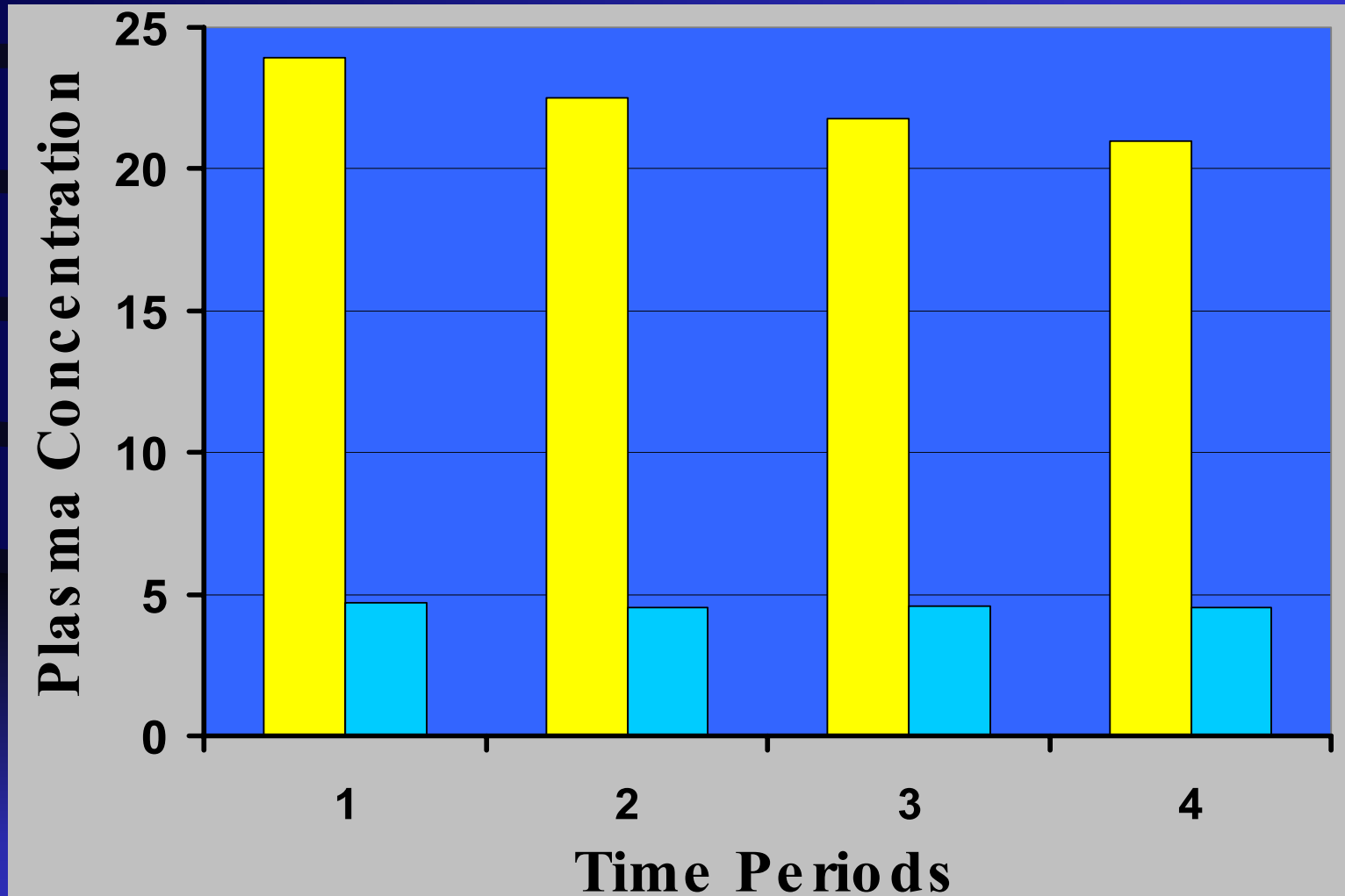
Clearance of Methadone

During and After Pregnancy



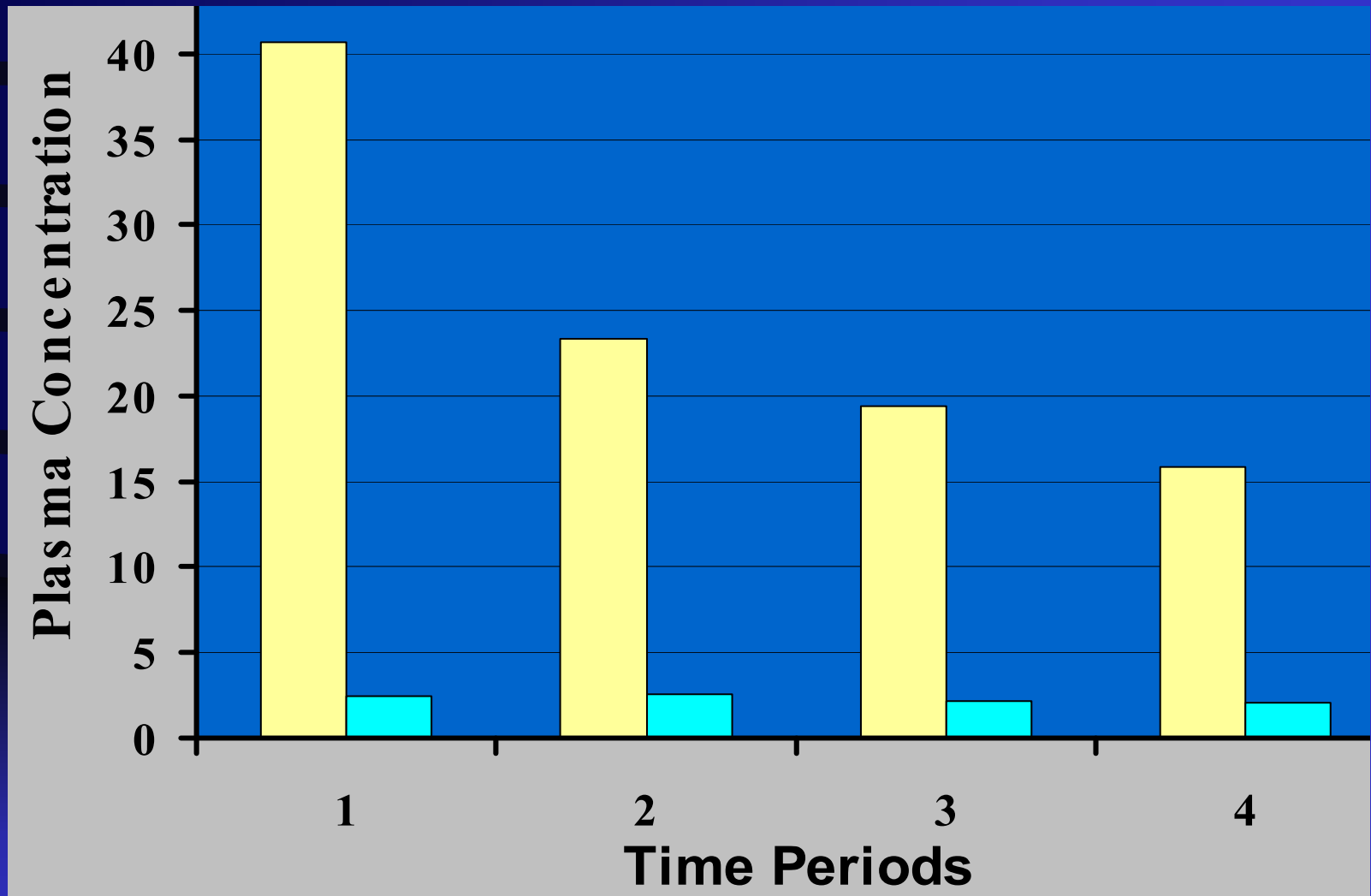
Pond SM, et al. Journ Pharm Exp Ther 1978; 233:1-6.

Carbamazepine Plasma Concentrations During Pregnancy



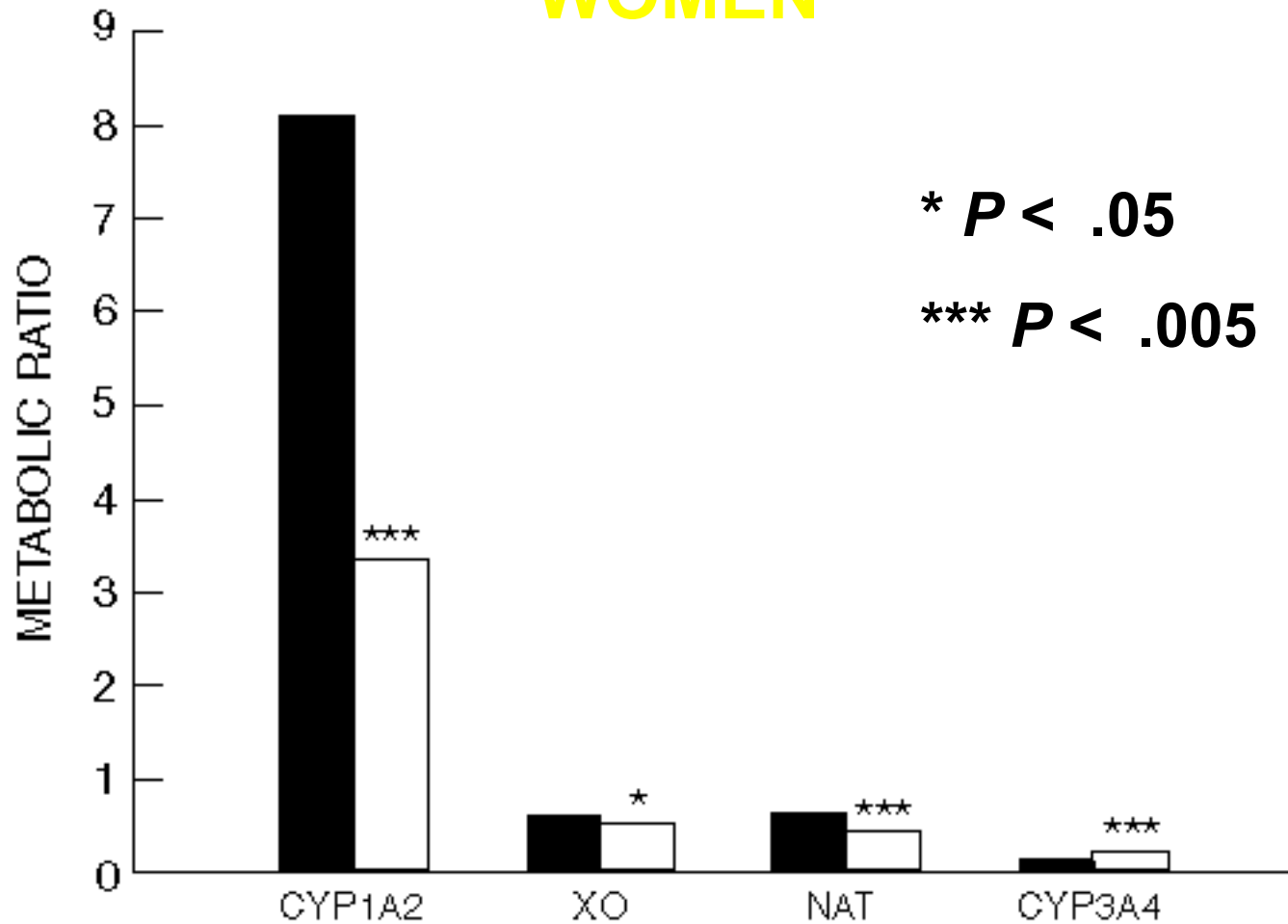
Tomsom T, et al. Epilepsia 1994; 35:122-30.

Phenytoin Plasma Concentrations in Pregnancy



Tomsom T, et al. *Epilepsia* 1994; 35:122-30.

CAFFEINE METABOLITE / PARENT DRUG RATIOS IN PREGNANT AND NON-PREGNANT WOMEN



Bologa M, et al. J Pharmacol Exp Ther 1991;257:735-40.

Pharmacokinetics of Cefuroxime in Pregnancy

Patient Category	$V_D(L)$	Cl(ml/min)	T(1/2)
Pregnant	17.8 \pm 1.9	282 \pm 34*	44 \pm 5*
At Delivery	19.3 \pm 3.1	259 \pm 35*	52 \pm 10
Postpartum	16.3 \pm 2.1	198 \pm 27	58 \pm 8

*p<0.05 on comparison to PP

Tobramycin Pharmacokinetics

- Cl higher in mid-trimester with a corresponding shorter half-life
- Cl lower in the third trimester with a corresponding longer half-life
- V_d / kg shows no change

Bourget P, et al. J Clin Pharm Ther 1991;16:167-76

Heparin Pharmacokinetics during Pregnancy

- Shorter time to peak heparin concentration and effect
- Lower peak effect

Brancazio et al. Am J Obstet Gynecol 1995; 173: 1240.

Enoxaprin Pharmacokinetics during Pregnancy

- T_{\max} shows no change
- C_{\max} lower during pregnancy
- Cl decreases in late pregnancy
- Lower anti-factor Xa activity
- AUC lower during pregnancy

Casele, et al. Am J Obstet Gynecol 1999; 181: 1113.

Maternal Physiologic Changes Altering PK of Drugs

- **Volume expansion**
- **Protein binding**
- **Clearance changes**
- **Gastrointestinal changes**

Oral Ampicillin Pharmacokinetics in Pregnancy

Parameter	Pregnant	Nonpregnant
AUC(cm ²)	8.2 _± 4.1	12.6 _± 4.3*
Peak Level (µg/ml)	2.2 _± 1.0	3.7 _± 1.5*
Bioavailability (%)	45.6 _± 20.2	48.1 _± 19.3**
		*p<0.001 **NS

Philipson A. J Inf Dis 1977;136:370-6.

PK of Oral Valacyclovir & Acyclovir

- The pro-drug Valacyclovir converted by first pass metabolism to Acyclovir
- Non-pregnant Valacyclovir gives 3 - 5 times higher plasma level as Acyclovir
- Valacyclovir PK study in pregnancy gave plasma levels 3 times higher than Acylovir

Kimberlin DF, et al. Amer J Obstet Gynecol 1998; 179: 846

Peripartum Pharmacologic Considerations

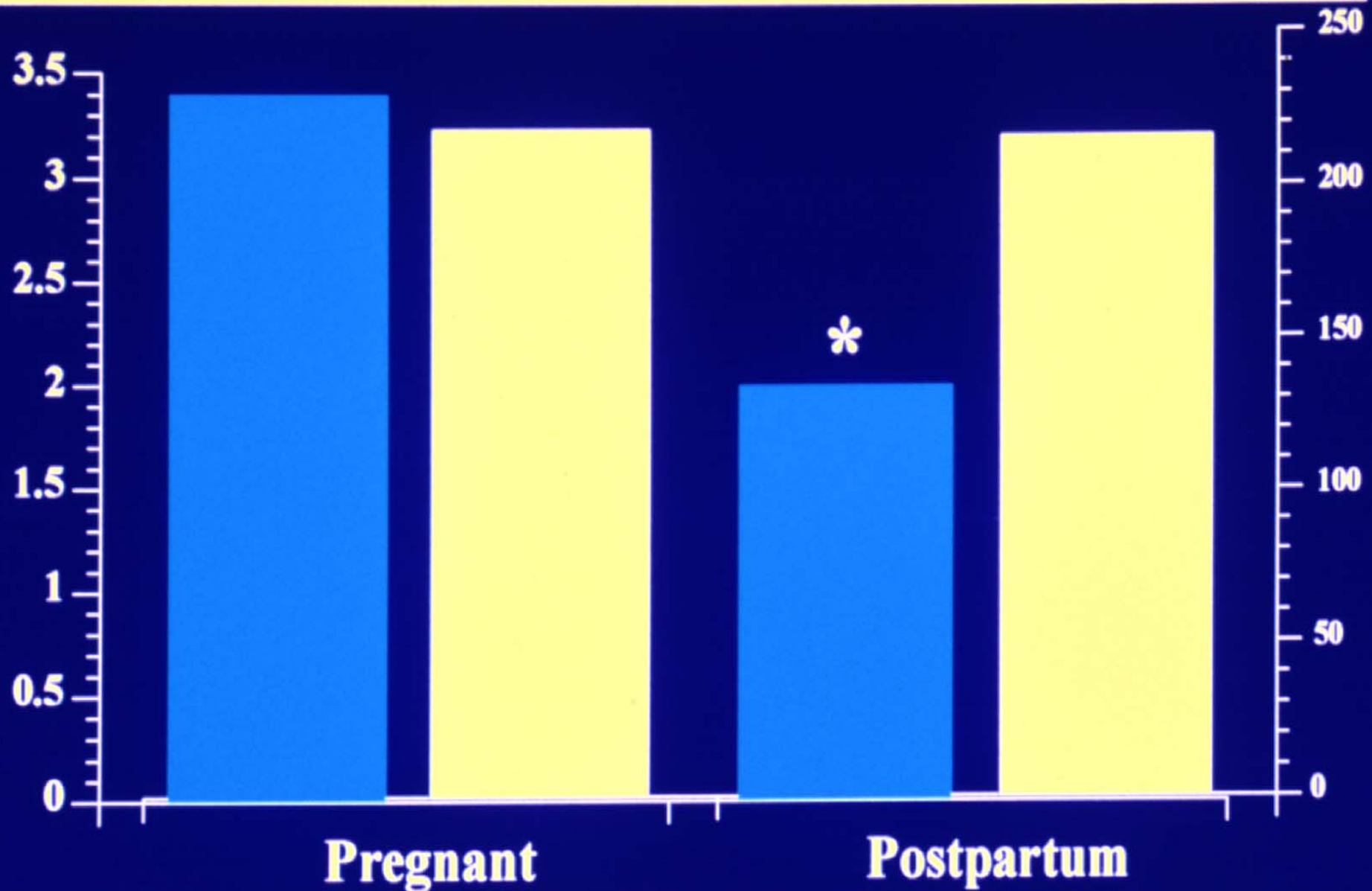
- Increased cardiac output
- Blood flow changes
- Uterine contractions
- ? Pharmacodynamic changes

Pharmacokinetics of Cefuroxime in Pregnancy

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*p<0.05 on comparison to PP

Morphine Pharmacokinetics During Labor



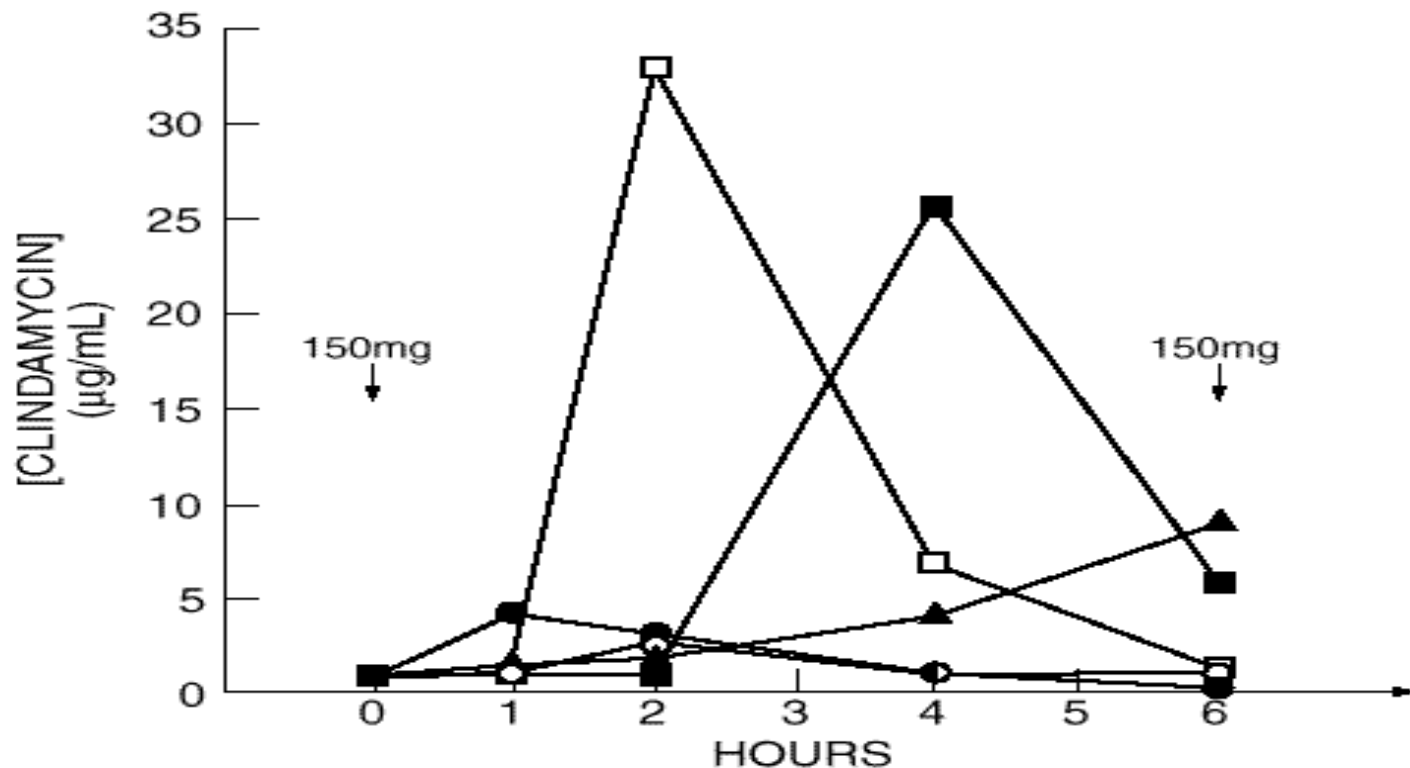
Gerdin E, et al. J Perinat Med 1990; 18: 479-487.

* $p < 0.05$

Postpartum PK Considerations

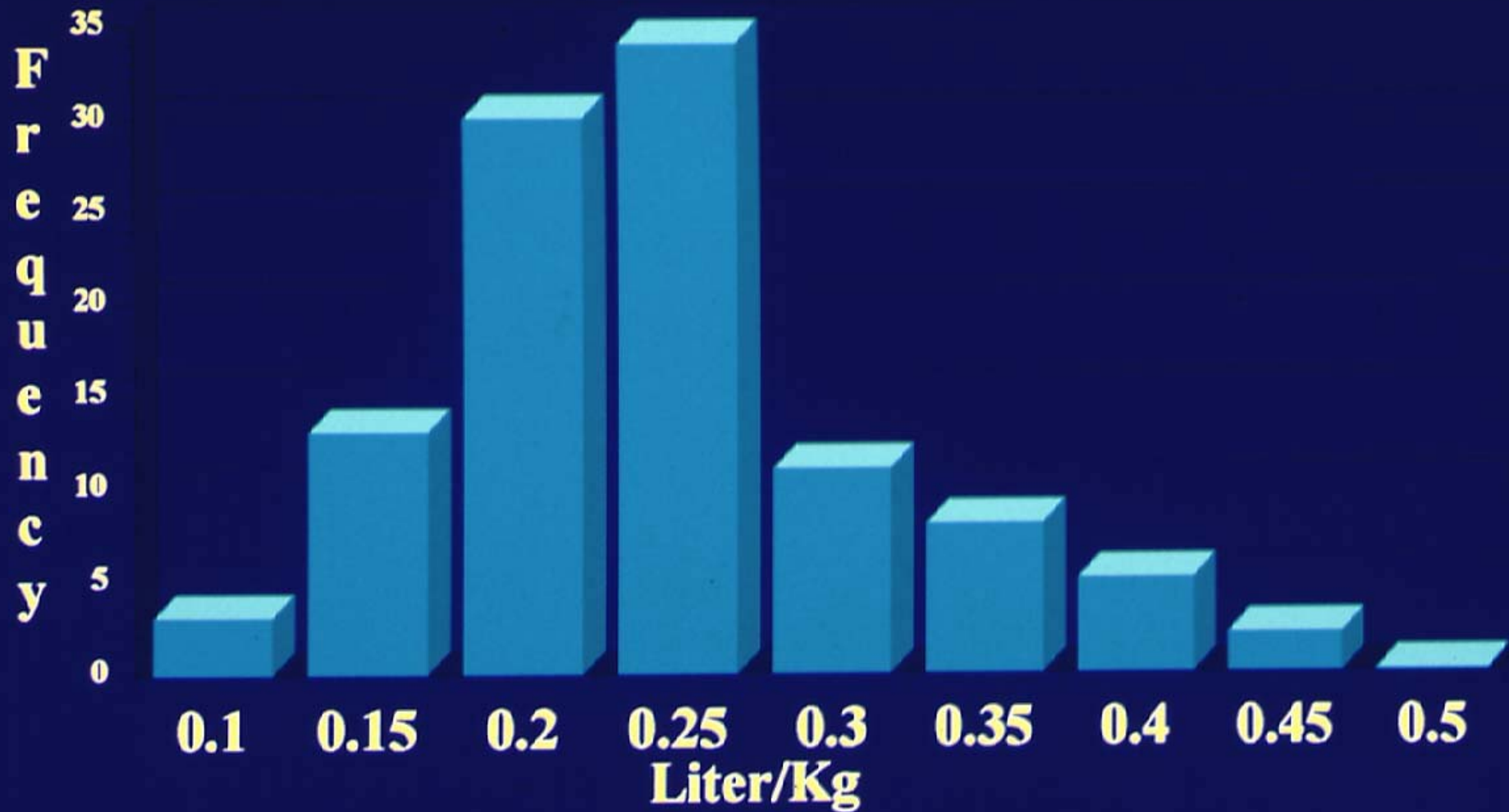
- Increased cardiac output maintained
- GFR increased
- Diuresis
- Breastfeeding
- Great variability

Postpartum Clindamycin Pharmacokinetics



Steen B, et al. Br J Clin Pharmacol 1982; 13: 661.

Postpartum Gentamicin Distribution Volume



Del Priore Obstet Gynecol 1996; 87: 994

Drug Studies for Pregnancy

- **Pregnancy Specific Drugs**
 - **Tocolytic agents**
 - **Oxytocic agents**
 - **Eclampsia agents**
- **Drugs commonly used by women of childbearing potential**
 - **Antidepressants**
 - **Asthma drugs**

Technical Considerations

- **Ethical and IRB concerns**
- **Serial studies**
 - **Spanning pregnancy**
 - **Specific to peripartum period**
 - **Controls**

Study Design

- **Use population PK analysis**
- **Incorporate in vitro protein binding studies**
- **Use stable isotopes for bioavailability studies**
- **Use established tracer substances as reference markers**

Teratogenesis

General Principles of Teratology

- Teratogens act with specificity
- Teratogens demonstrate a dose-response relationship
- Teratogens must reach the conceptus
- Effects depend upon the development stage when exposed
- Genotype of mother and fetus effect susceptibility

General Principles of Teratology

- Teratogens act with specificity

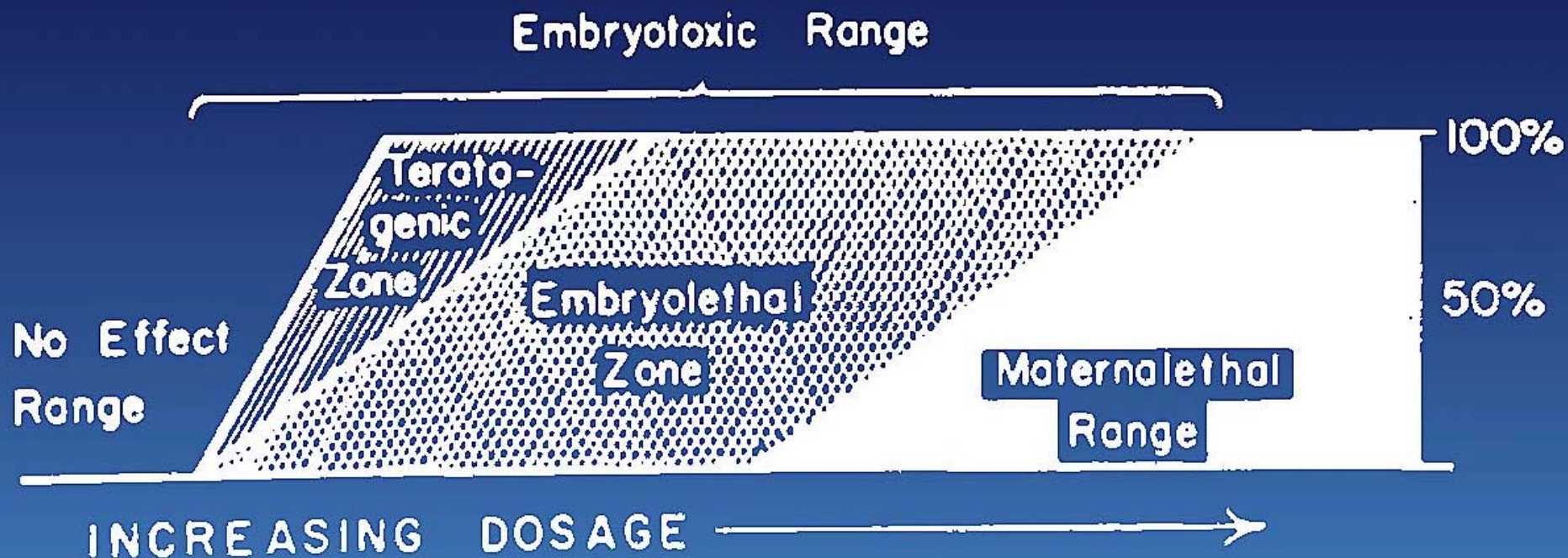
PHOCOMELIA DUE TO THALIDOMIDE



General Principles of Teratology

- **Teratogens act with specificity**
- Teratogens demonstrate a dose-response relationship

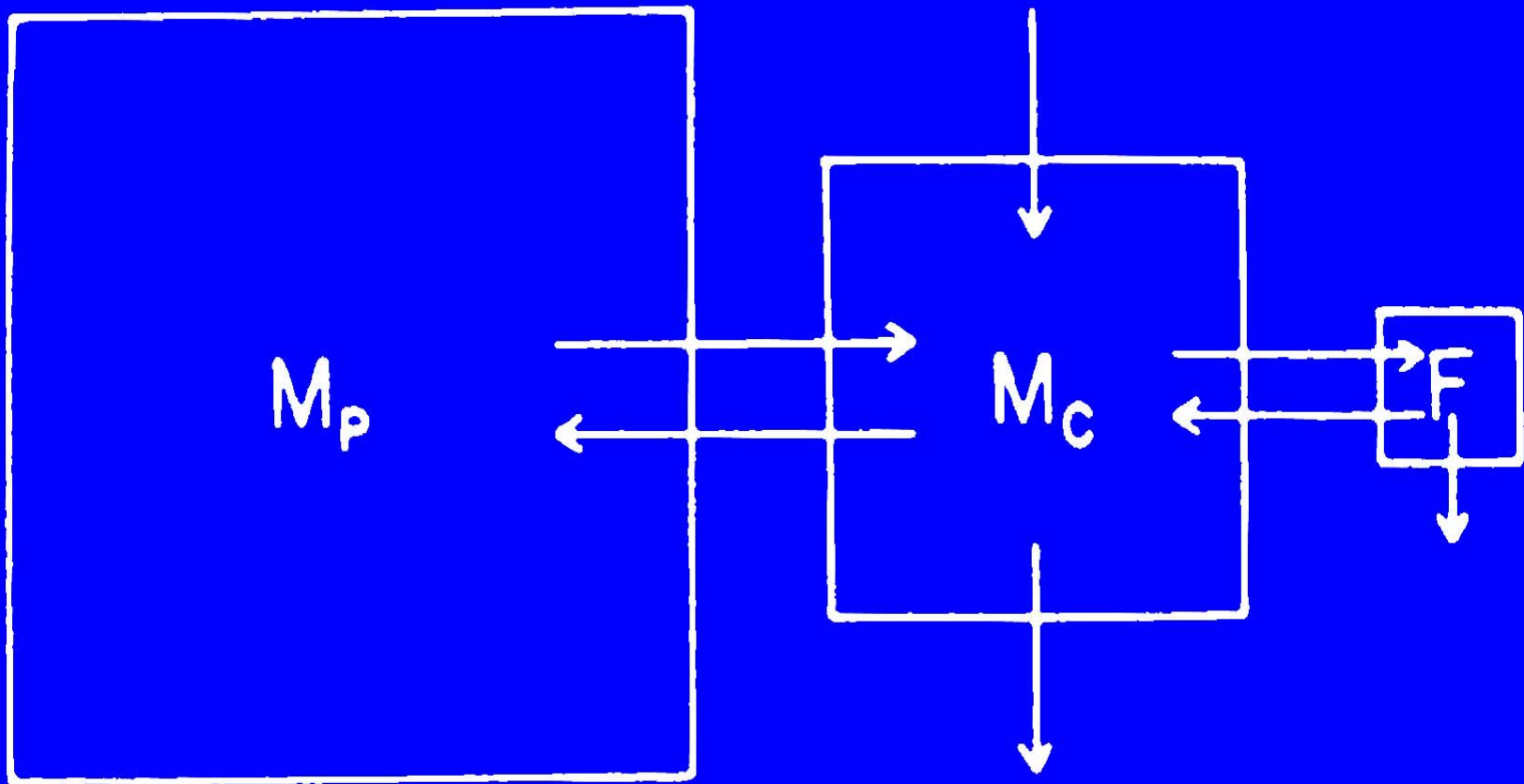
DOSE-RESPONSE RELATIONSHIPS



General Principles of Teratology

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PHARMACOKINETIC MODEL OF MATERNAL-FETAL TRANSPORT



General Principles of Teratology

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All or Nothing Period

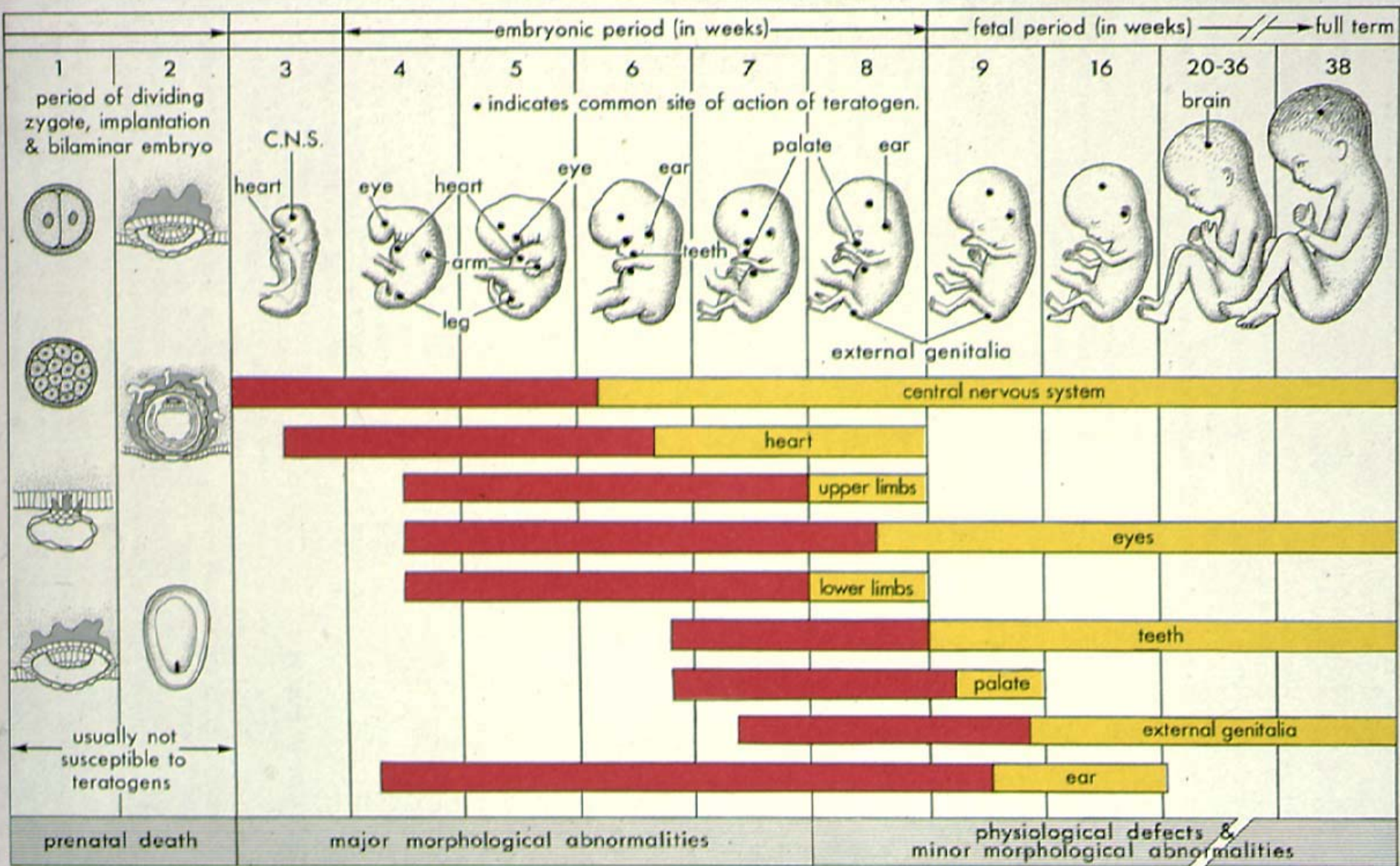


Figure 8-14 Schematic illustration of the critical periods in human development. During the first two weeks of development, the embryo is usually not susceptible to teratogens. During these predifferentiation stages, a

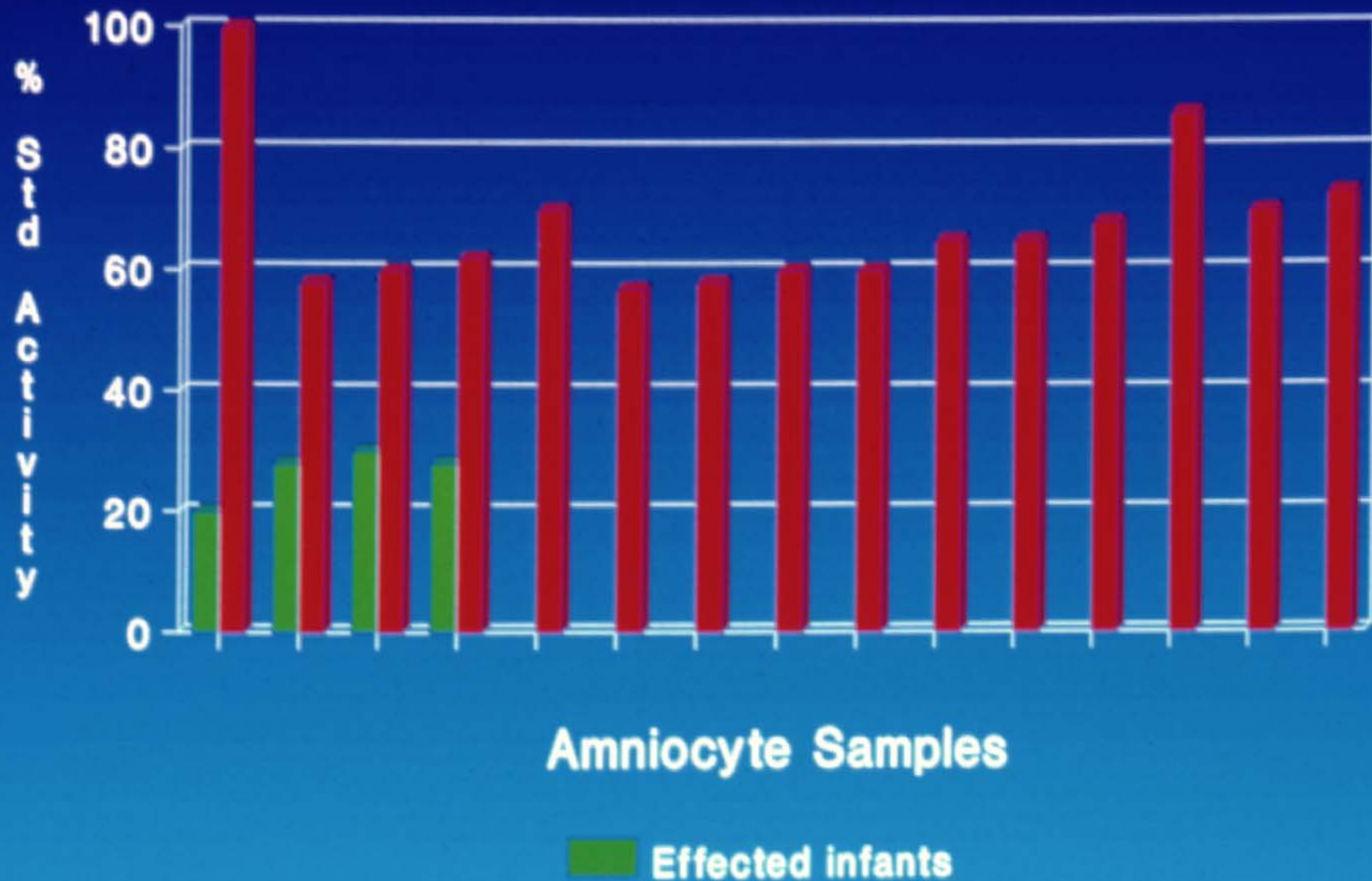
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Phenytoin

- **Animal evidence for an arene oxide (epoxide) reactive metabolite**
- **Genetic susceptibility to the Dilantin Syndrome related to variation in Epoxide hydrolase activity**

Identification of the Fetus at Risk



Genetic Polymorphisms

- Increased risk of clefting in fetuses carrying atypical allele for transforming growth factor α whose mothers smoke
- Decreased risk for fetal alcohol syndrome in African American women carrying alcohol dehydrogenase isoform 2

Mechanisms of Teratogenesis

- All theoretical
- Most not understood well
- Implications of a genetic component

Thalidomide

- **Thalidomide causes DNA oxidation in animals susceptible to teratogenesis**
- **Pre-treatment with PBN (free radical trapping agent) reduced thalidomide embryopathy**
- **Suggesting that the mechanism is free radical-mediated oxidative DNA damage**

Parman T, et al. Nature Medicine 1999; 5: 582

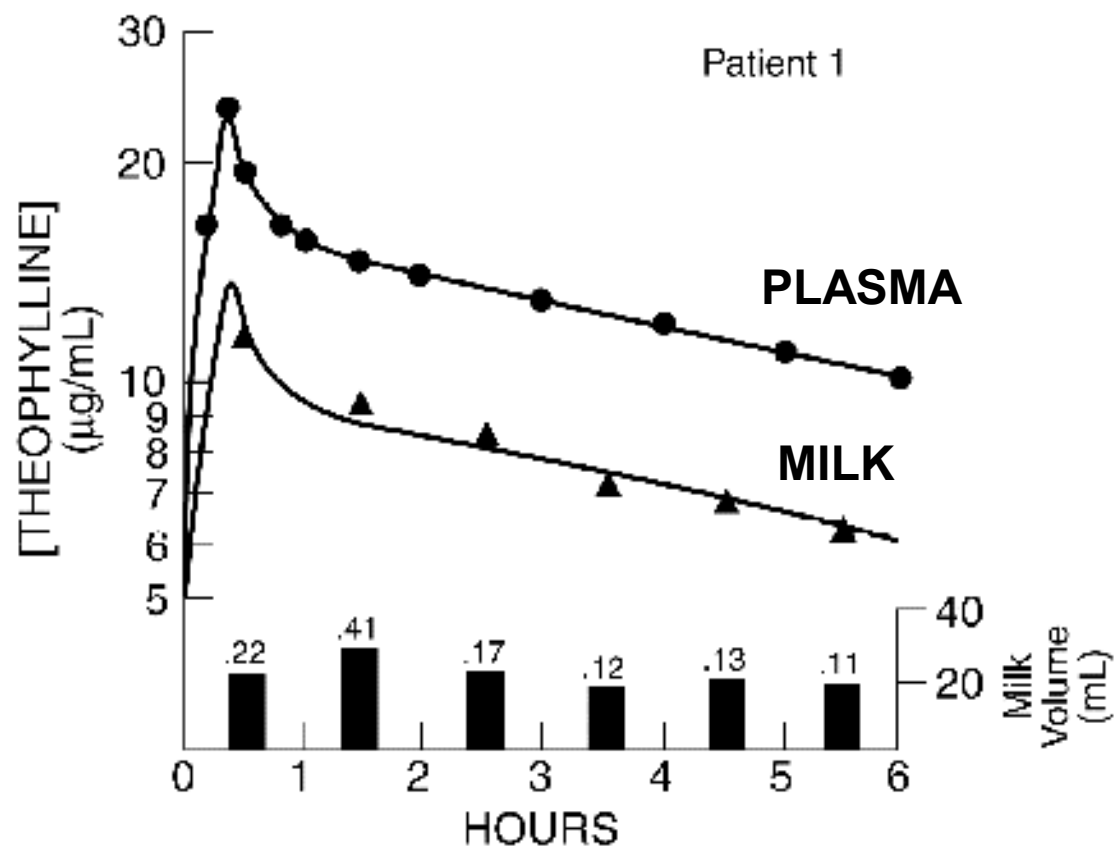
Evaluation of Drugs in Breast Milk

- Measure the M / P ratio
- Estimate breast milk dose
- Estimate infant dose
- Measure blood level in the infant

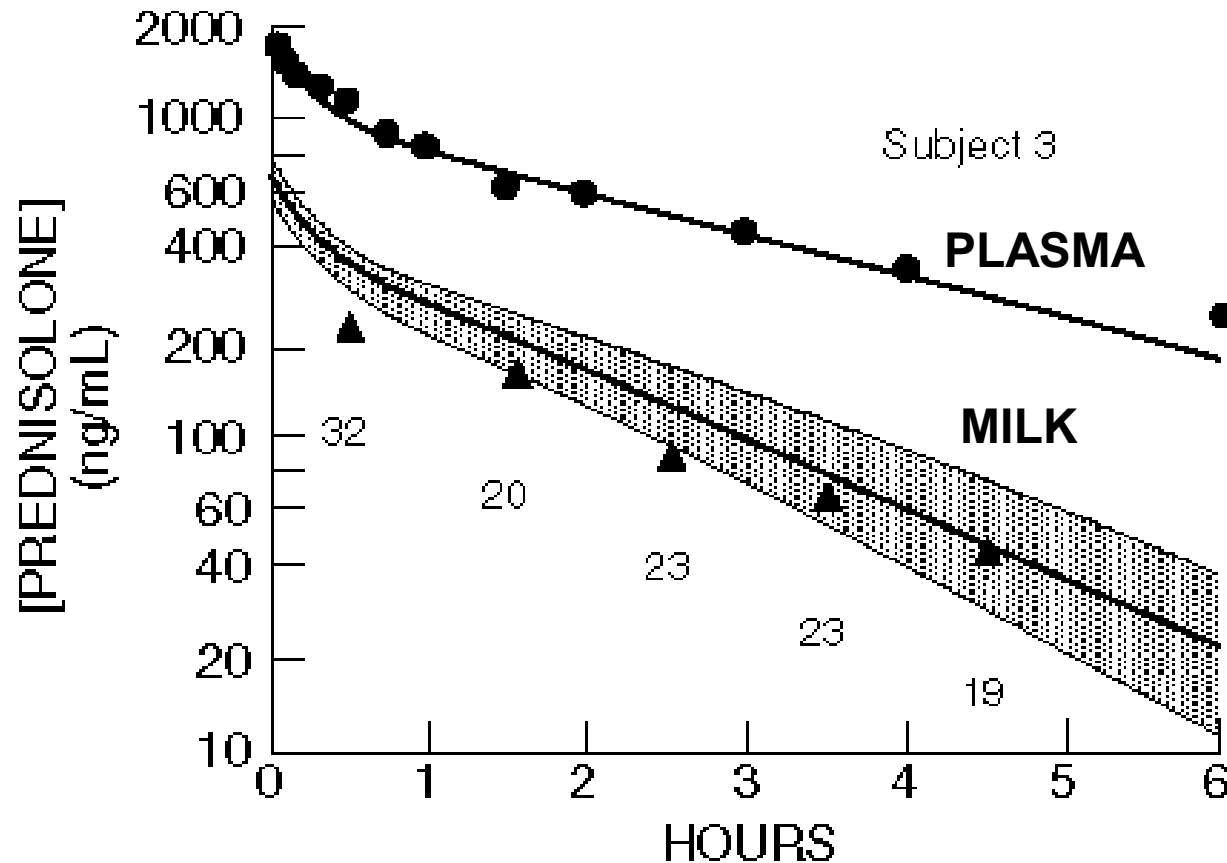
Drugs in Breast Milk

- Free drug transferred into milk
- Milk concentrations usually less than serum concentrations
- Exchange is bi-directional

KINETIC ANALYSIS OF THEOPHYLLINE PLASMA AND MILK CONCENTRATIONS



KINETIC ANALYSIS OF PREDNISOLONE PLASMA AND MILK CONCENTRATIONS



SHADED AREA IS EXPECTED RANGE OF UNBOUND PLASMA CONCENTRATIONS

Factors Effecting the Milk / Plasma Concentration Ratio

- **Maternal protein binding**
- **Protein binding in milk**
- **Lipid solubility of drug**
- **Physiochemical factors of drug effecting diffusion**

Drugs Contraindicated during Lactation

- Antineoplastics
- Immune suppressants
- Ergot Alkaloids
- Gold
- Iodine
- Lithium carbonate
- Radiopharmaceuticals
- Social drugs & drugs of abuse
- Certain antibiotics

General Recommendations

- **Drugs considered safe for pregnancy are usually safe during lactation**
- **Decrease the drug dose to the infant by feeding just prior to a dose**
- **Infant blood levels can be monitored and should be less than therapeutic**